```
=> d his 1

     (FILE 'HCAPLUS' ENTERED AT 16:36:02 ON 22 JUL 2004)
L15            3 S L14 AND CYCLIC

=> d que l15
L13            4 SEA FILE=REGISTRY 'GLA'LYENVGM/SQSP
L14            3 SEA FILE=HCAPLUS L13
L15            3 SEA FILE=HCAPLUS L14 AND CYCLIC


=> fil reg
FILE 'REGISTRY' ENTERED AT 16:38:46 ON 22 JUL 2004
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provided by InfoChem.

STRUCTURE FILE UPDATES:   21 JUL 2004  HIGHEST RN 714195-59-2
DICTIONARY FILE UPDATES:  21 JUL 2004  HIGHEST RN 714195-59-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sqide l13 1-4

L13  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   311791-39-6  REGISTRY
CN   L-Proline, 4-carboxy-N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-
     tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-
     tyrosyl-L-cysteinyl-L-alanyl-L-alanyl-L-valyl-L-alanyl-L-leucyl-L-leucyl-L-
     prolyl-L-alanyl-L-valyl-L-leucyl-L-leucyl-L-alanyl-L-leucyl-L-leucyl-L-
     alanyl-, cyclic (1→10)-thioether (9CI)  (CA INDEX NAME)
FS   PROTEIN SEQUENCE; STEREOSEARCH
SQL  26
NTE  modified (modifications unspecified)
-----------------------------------------------------------------------
 type            ------ location ------         description
-----------------------------------------------------------------------
bridge           Gla-1       - Cys-10      lactam
uncommon         Gla-1           -         -
-----------------------------------------------------------------------

SEQ      1 XLYENVGMYC AAVALLPAVL LALLAP
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HITS AT:   1-8
MF   C130 H205 N27 O37 S2
SR   CA
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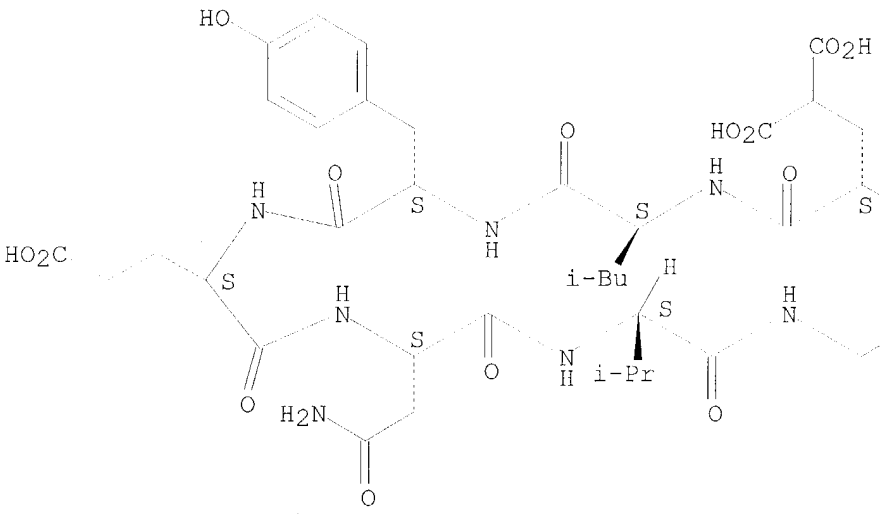
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study)

Absolute stereochemistry.

PAGE 1-A



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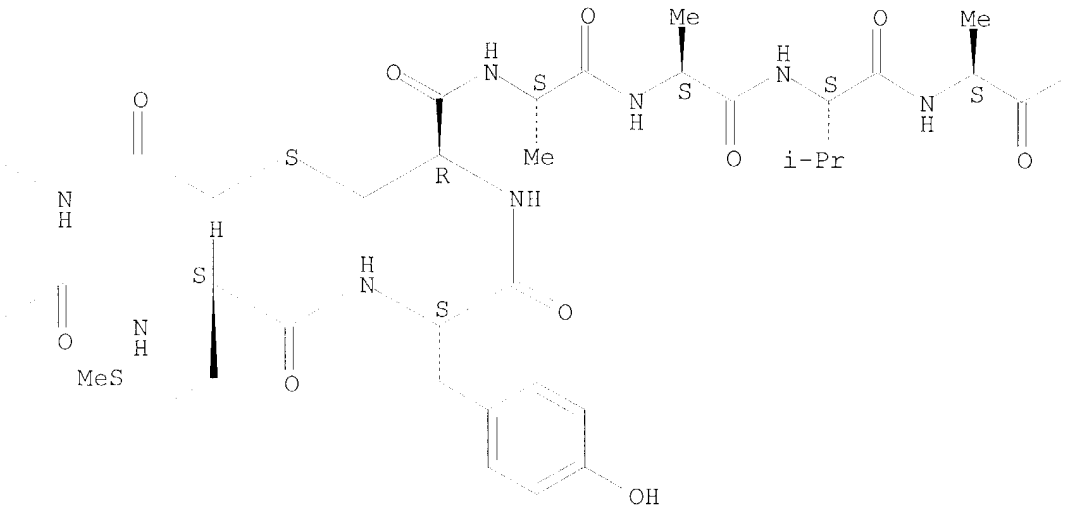

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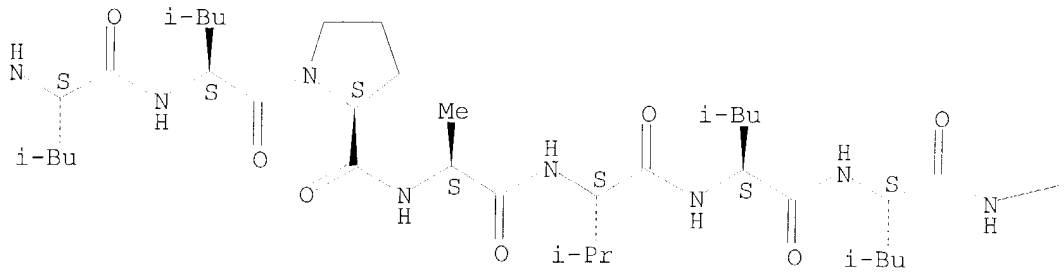

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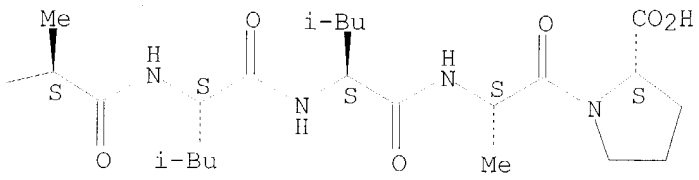


3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 311791-09-0 REGISTRY
CN L-Norvalinamide, 4-carboxy-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-5-carboxy-, (10→1)-lactam (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 10
NTE modified (modifications unspecified)

type	------ location ------		description
bridge	Gla-1	- Aad-10	lactam
uncommon	Gla-1	-	-
uncommon	Aad-10	-	-

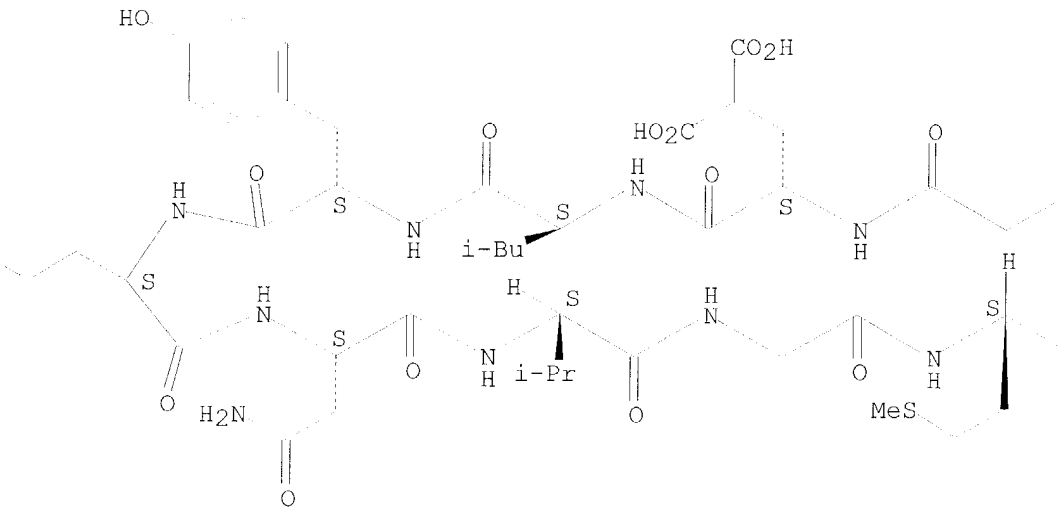
SEQ 1 XLYENVGMYX
========
HITS AT: 1-8
MF C57 H80 N12 O20 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

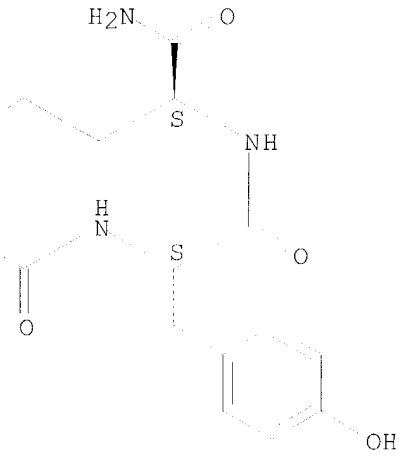
Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B





2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 311791-07-8 REGISTRY
CN L-Serinamide, hydroxyacetyl-4-carboxy-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-, cyclic (1→11)-ether (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 10
NTE modified (modifications unspecified)

type	------ location ------		description
bridge	Gla-1	- Ser-10	lactam
uncommon	Gla-1	-	-

SEQ 1 XLYENVGMYS
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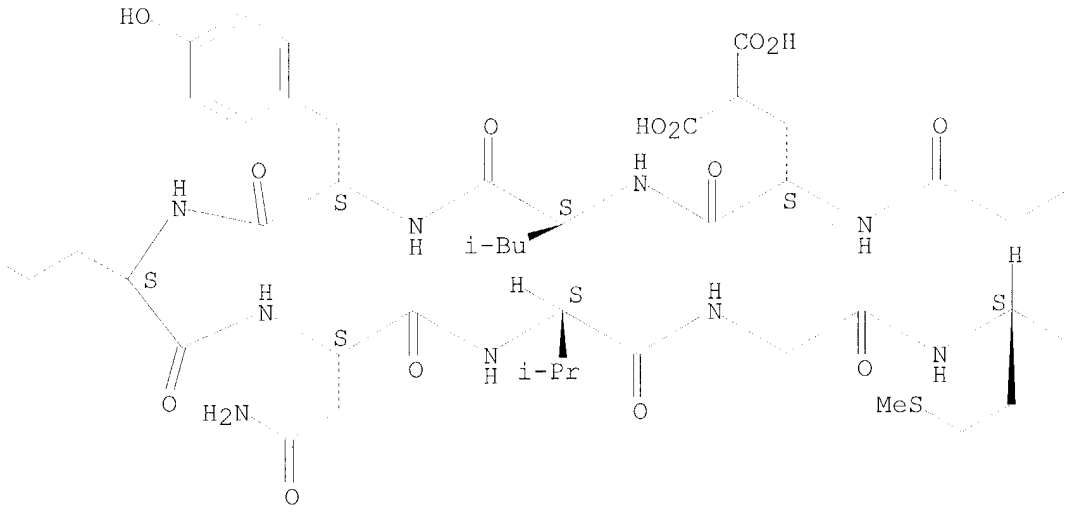
HITS AT: 1-8
MF C56 H78 N12 O21 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

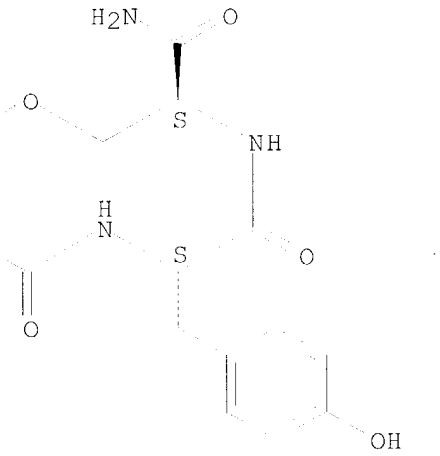
Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B





2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 311791-05-6 REGISTRY
CN L-Cysteinamide, 4-carboxy-N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 10
NTE modified (modifications unspecified)

type	------ location ------		description
bridge	Gla-1	- Ala-10	lactam
uncommon	Gla-1	-	-

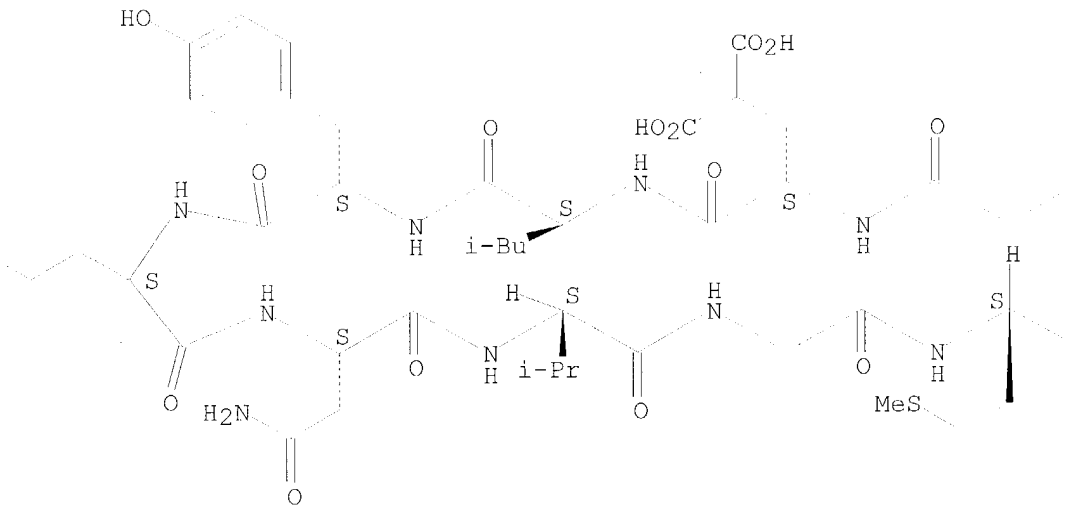
SEQ 1 XLYENVGMYA
========
HITS AT: 1-8
MF C56 H78 N12 O21 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

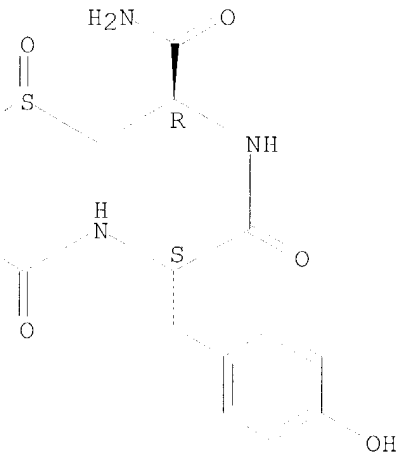
Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B





2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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FILE COVERS 1907 - 22 Jul 2004 VOL 141 ISS 4
FILE LAST UPDATED: 21 Jul 2004 (20040721/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L15 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:766786 HCAPLUS
DOCUMENT NUMBER: 140:55178
TITLE: Potentiating effect of distant sites in

non-phosphorylated **cyclic** peptide antagonists of the Grb2-SH2 domain

AUTHOR(S): Long, Ya-Qiu; Guo, Ribo; Luo, Juliet H.; Yang, Dajun; Roller, Peter P.

CORPORATE SOURCE: Shanghai Institutes for Biological Sciences, Shanghai Institute of Materia Medica, State Key Laboratory of Drug Research, Chinese Academy of Sciences, Shanghai, 201203, Peop. Rep. China

SOURCE: Biochemical and Biophysical Research Communications (2003), 310(2), 334-340
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Without the presence of a phosphotyrosyl group, a phage library derived non-phosphorylated **cyclic** peptide ligand of Grb2-SH2 domain attributed its high affinity and specificity to well-defined and highly favored interactions of its structural elements with the binding pocket of the protein. We have disclosed a significant compensatory role of the Glu2- sidechain for the absence of the phosphate functionality on Tyr0 in the peptide ligand, cyclo(CH2CO-Glu2--Leu-Tyr0-Glu-Asn-Val-Gly-Met5+-Tyr-Cys)-amide (termed G1TE). In this study, we report the importance of hydrophobic residue at the Tyr + 5 site in G1TE. Both acidic and basic amino acid substitutes are disfavored at this position, and replacement of Met with β-tert-butyl-Ala was found to improve the antagonist properties. Besides, the polarity of the cyclization linkage was implicated as important in stabilizing the favored binding conformation. Oxidation of the thioether linkage into sulfoxide facilitated the binding to Grb2-SH2 markedly. Simultaneous modification of the three distant sites within G1TE provided the best agent with an IC50 of 220 nM, which is among the most potent non-phosphorous- and non-phosphotyrosine-mimic containing Grb2-SH2 domain inhibitors yet reported. This potent peptidomimetic provides a novel template for the development of chemotherapeutic agents for the treatment of erbB2-related cancer. Biol. assays on G1TE(Gla2-) in which the original residue of Glu2- was substituted by γ-carboxyglutamic acid (Gla) indicated that it could inhibit the interaction between activated GF receptor and Grb2 protein in cell homogenates of MDA-MB-453 breast cancer cells at the 2 μM level. More significantly, both G1TE(Gla2-) alone and the conjugate of G1TE(Gla2-) with a peptide carrier can effectively inhibit intracellular association of erbB2 and Grb2 in the same cell lines with IC50 of 50 and 2 μM, resp.

IT **311791-39-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(potentiating effect of distant sites in non-phosphorylated **cyclic** peptide antagonists of Grb2-SH2 domain)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:319477 HCAPLUS

DOCUMENT NUMBER: 138:287983

TITLE: Redox-stable, non-phosphorylated **cyclic** peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions, methods of synthesis, and use

INVENTOR(S): Roller, Peter P.; Long, Ya-Qiu; Lung, Feng-Di T.; King, C. Richter; Yang, Dajun

PATENT ASSIGNEE(S): The Government of the United States of America, USA

SOURCE: U.S. Pat. Appl. Publ., 10 pp., Cont.-in-part of Appl.

No. PCT/US00/15201.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003078368	A1	20030424	US 2001-998350	20011130
WO 2000073326	A2	20001207	WO 2000-US15201	20000602
WO 2000073326	A3	20010525		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-137187P P 19990602
WO 2000-US15201 A2 20000602
OTHER SOURCE(S): MARPAT 138:287983
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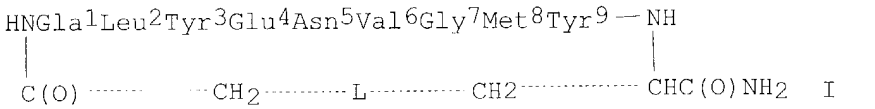

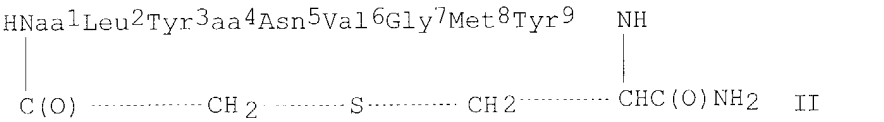

AB The invention provides I (L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Glu4, Val6, Met8 and Tyr9 is modified). Also provided are compds. II [aa1 = Adi and aa4 = Glu, or each of aa1 and aa4 = Adi; L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Val6, Met8 and Tyr9 is modified]. Compds. I and II (and their conjugates) bind to an SH2 domain in a protein comprising an SH2 domain, are non-phosphorylated, are redox-stable in vivo, and are characterized by an IC50 in vivo of less than about 4.0 < mM with respect to the SH2 domain in Grb2. Upon binding to the SH2 domain of Grb2, a compound as described above has a turn conformation. Also provided are a conjugate comprising a compound as described above and a carrier agent, a composition comprising (i) a compound or a conjugate as described above and (ii) a carrier, a method of inhibiting binding of an SH2 domain in a protein comprising an SH2 domain to a target protein in an animal, where the SH2 domain is contacted with a target protein-binding inhibiting effective amount of a compound or a conjugate as described above, and a method of synthesizing such conjugates. Thus, cyclo(CH2CO-Adi1-Leu2-Tyr3-Glu4-Asn5-Val6-Gly7-Met8-Tyr9-Cys)-amide was synthesized by the solid-phase method and showed IC50 = 3.45 ± 0.15 for binding affinity to the SH2

domain of Grb2.
IT **311791-39-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of redox-stable, non-phosphorylated **cyclic** peptide inhibitors of SH2 domain binding to target protein)
IT **311791-05-6 311791-05-6D**, amino acid-modified derivs. and conjugates **311791-07-8 311791-07-8D**, amino acid-modified derivs. and conjugates **311791-09-0 311791-09-0D**, amino acid-modified derivs. and conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of redox-stable, non-phosphorylated **cyclic** peptide inhibitors of SH2 domain binding to target protein)

L15 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:861699 HCAPLUS
DOCUMENT NUMBER: 134:25345
TITLE: Redox-stable, non-phosphorylated **cyclic** peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions, methods of synthesis, and use
INVENTOR(S): Roller, Peter P.; Long, Ya-Qui; Lung, Feng-Di T.; King, C. Richter; Yang, Dajun
PATENT ASSIGNEE(S): Government of the United States of America, Represented by the Secretary, Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073326	A2	20001207	WO 2000-US15201	20000602
WO 2000073326	A3	20010525		
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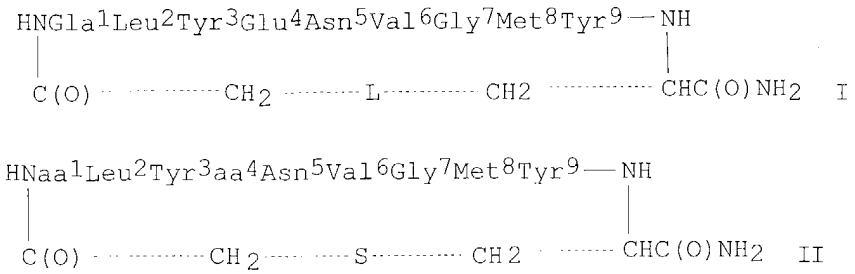
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003078368	A1	20030424	US 2001-998350	20011130

PRIORITY APPLN. INFO.: US 1999-137187P P 19990602
WO 2000-US15201 A2 20000602

OTHER SOURCE(S): MARPAT 134:25345
GI



AB The invention provides I (L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Glu4, Val6, Met8 and Tyr9 is modified). Also provided is compound II [aa1 = Adi and aa4 = Glu, or each of aa1 and aa4= Adi; L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Val6, Met8 and Tyr9 is modified]. The above compds. (and their conjugates) bind to an SH2 domain in a protein comprising an SH2 domain, are non-phosphorylated, are redox-stable in vivo, and are characterized by an IC50 in vivo of less than about 4.0 <mM with respect to the SH2 domain in Grb2. Upon binding to the SH2 domain of Grb2, a compound as described above has a turn conformation. Optionally, there is a conservative or neutral amino acid substitution at either one or both of Leu2 and Gly7. Also provided are a conjugate comprising a compound as described above and a carrier agent, a composition comprising (i) a compound or a conjugate as described above and (ii) a carrier, a method of inhibiting binding of an SH2 domain in a protein comprising an SH2 domain to a target protein in an animal, wherein the SH2 domain is contacted with a target protein-binding inhibiting effective amount of a compound or a conjugate as described above, and a method of synthesizing such conjugates.

IT **311791-39-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(redox-stable, non-phosphorylated **cyclic** peptide inhibitors of SH2 domain binding to target protein, conjugates, compns., preparation, and use)

IT **311791-05-6 311791-05-6D**, amino acid-modified derivs. and conjugates **311791-07-8 311791-07-8D**, amino acid-modified derivs. and conjugates **311791-09-0 311791-09-0D**, amino acid-modified derivs. and conjugates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(redox-stable, non-phosphorylated **cyclic** peptide inhibitors of SH2 domain binding to target protein, conjugates, compns., preparation, and use)